A review of hypoxaemia in the anaesthetised horse: predisposing factors, consequences and management.

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Abstract

Objectives

To discuss how hypoxaemia might be harmful and why the horse is particularly predisposed to developing it. To review the strategies that are used to manage hypoxaemia in anaesthetised horses, to describe how successful these strategies are and the adverse events associated with them.

Databases used

Google Scholar and PubMed using the search terms – horse; pony; exercise; anaesthesia; hypoxaemia; oxygen; mortality; morbidity; ventilation perfusion mismatch.

Conclusions

Although there is no evidence that hypoxaemia is associated with increased morbidity and mortality in anaesthetised horses, most anaesthetists would agree that it is important to recognise and prevent or treat it. The favourable anatomical and physiological adaptations of the horse for exercise, adversely affect gas exchange once the animal is recumbent. Hypoxaemia is recognised more frequently than in other domestic species during general anaesthesia, although its incidence in healthy horses remains unreported. The management of hypoxaemia in anaesthetised horses is challenging and often unsuccessful. Positive pressure ventilation strategies to address alveolar atelectasis in humans have been modified for implementation in the recumbent anaesthetised horse, but are often accompanied by unpredictable and unacceptable cardiopulmonary adverse effects, and some strategies are difficult or impossible to achieve in adult horses. Furthermore, the anticipated beneficial effects of these techniques are inconsistent. Increasing the inspired fraction of oxygen during anaesthesia is often unsuccessful since much of the impairment in gas exchange is a direct result of shunt. Alternative approaches to the problem involve the manipulation of pulmonary blood away from

atelectatic regions of lung to better ventilated areas. However, further work is essential, with particular focus upon survival associated with general anaesthesia in the horse, before any technique can be accepted into widespread clinical use.

Keywords: horses, hypoxaemia, anaesthesia, management

Introduction

For the equine anaesthetist, minimising patient mortality and morbidity remains a priority, and it is important to identify the causes to reduce the risk associated with anaesthesia. Mortality associated with anaesthesia in healthy horses varies between reports but can be as high as 0.9% (Young & Taylor 1993; Johnston et al. 2002; Bidwell et al. 2007; Dugdale et al. 2016). In animals with systemic disease, death rates are much higher (Pascoe et al. 1983; Johnston et al. 2002). General risk factors include the duration of anaesthesia with cumulative effects of hypotension, hypoxaemia and acid-base derangements (Johnston et al. 2002). In the horse, general anaesthesia is frequently accompanied by impairment of pulmonary function and a resultant low arterial oxygen tension or partial pressure (PaO_2), which is challenging to treat (Nyman & Hedenstierna 1989; Nyman et al. 2012), although its incidence in the general horse population is unreported. In horses anaesthetised for colic surgery, the incidence of hypoxaemia (using a definition of PaO_2 less than 80 mmHg (10.7 kPa)) has been reported as approximately 13% (Pascoe et al. 1983).

Currently, evidence that hypoxaemia (defined as a PaO_2 of less than 60 mmHg (8.0 kPa)) occurring under general anaesthesia is harmful is sparse. The circulatory effects of experimentally induced hypoxaemia in anaesthetised horses have been described (Steffey et al. 1992; Whitehair et al. 1996). During halothane anaesthesia, heart rate and cardiac output increase but total peripheral resistance, arterial blood pressure and oxygen delivery decrease, regardless of ventilatory mode (Steffey et al. 1992). During periods of hypoxaemia, circulatory function is worse during controlled ventilation (Steffey et al 1992) and when halothane is used compared with isoflurane (Whitehair et al. 1996). Since global oxygen delivery is a function of cardiac output and oxygen content, a reduction in tissue oxygenation may occur during periods of hypoxaemia.

Coronary blood flow increases by up to 35% in human volunteers subjected to arterial haemoglobin oxygen saturations ($Sa0_2$) of 70 – 75% (Grubbström et al. 1993). When the reserve is insufficient to meet demand, lactate is produced within the myocardium, which adversely affects metabolic, mechanical and electrical activity resulting in a fall in contractility and therefore, output, from the heart (Allen & Orchard 1987). It is logical to assume that similar effects occur within the equine myocardium during periods of acute hypoxaemia, although the coronary reserve of the horse is unknown.

Brain function depends on a continuous supply of oxygen, as neurons do not have the ability to store it for later use. Brain injury in the face of hypoxia occurs because of: acidosis due to accumulation of lactic acid; intracellular accumulation of calcium; neurotoxic effects of excitatory neurotransmitters released in response to hypoxia; formation of oxygen reactive species (ROS) following re-oxygenation (Hopkins & Bigler 2001). Humans exposed to hypoxic environments experience loss of coordination, blurred vision, weakness and dizziness, which mimics mild brain injury, and the metabolic demand of neuronal tissue can increase by up to 15% during tasks that require cognitive function (Turner et al. 2015). Altered cognition in horses recovering from anaesthesia is likely to impact upon recovery quality, although this has not been documented or investigated.

In humans, surfactant production within the lung is reduced or altered during periods of hypoxaemia (Vaporidi et al. 2005), and may contribute to the development of acute respiratory distress syndrome (ARDS). The effect of hypoxaemia on surfactant in the equine lung is not known.

Hypoxaemia reduces calcium reuptake and release in the sarcoplasmic reticulum of skeletal muscle, decreasing cross-bridge activation and force output, possibly through lactate and hydrogen ion accumulation, or free radical production (Romer et al. 2006).

Muscle oxygenation is reduced during experimentally induced hypoxaemia in anaesthetised horses (Portier et al. 2009), and hypoxaemia-induced muscle injury is worse when halothane is used to anaesthetise horses compared with isoflurane (Whitehair et al. 1996). These effects may have a significant impact upon the ability of a horse to stand following anaesthesia.

Adequate delivery of oxygen to a wound is essential for optimal healing and resistance to infection in humans (Gottrup 2004). A low PaO_2 (less than 80 mmHg (10.7 kPa)) contributes to the development of surgical site infection in horses undergoing exploratory laparotomy (Costa-Farré et al 2014). Whilst wound breakdown and infection does not have direct relevance to anaesthetic risk, it may be linked to morbidity associated with perioperative hypoxaemia during general anaesthesia.

It might be interpreted from the information presented in the previous discussion, that these deleterious effects of hypoxaemia on the brain, cardiovascular and pulmonary systems, and on wound healing and surgical site infection, are partly responsible for the high morbidity and mortality associated with equine anaesthesia. However, the affinity of equine haemoglobin for oxygen is greater compared with humans making direct comparisons problematic (Clerbaux et al. 1993). Clearly, further work is required in this area to be certain of the consequences of intraoperative hypoxaemia in anaesthetised horses.

The horse at rest and during exercise

Commenting upon animal experimentation in 1865, the physiologist Claude Bernard said ‘certain animals offer favourable anatomical arrangements or special susceptibility to certain influences’ (Bernard 1865). The anatomical arrangement of the equine thorax is such that the majority of the lung is situated in a dorsal position, on top of the

abdominal viscera with a long, sloping diaphragm when the animal is standing, an anatomical adaptation in athletic species such as the horse. Once the animal is anaesthetised and turned on its back, this favourable arrangement becomes detrimental to pulmonary function, as most of the lung is now prone to compression (Hedenstierna et al. 2005). Thus, horses, more than any other domestic species, are susceptible to developing significant impairment of pulmonary function during recumbency and anaesthesia and a large right to left pulmonary shunt (Nyman et al. 2012). This pulmonary shunt has been estimated at 1% in standing horses and 19 and 33% in anaesthetised laterally and dorsally recumbent horses respectively (Nyman & Hedenstierna 1989).

Blood flows preferentially to the caudo-dorsal lung field in standing horses at rest and during exercise, and vessel reactivity in the dorsal lung fields of the horse demonstrate enhanced endothelial mediated vasorelaxation, compared with vessels from ventral regions (Pelletier et al. 1998; Stack et al. 2014). This dorsal vasorelaxation favours improved perfusion in these well-ventilated regions. Despite this adaptation, during strenuous exercise, thoroughbred horses have a lower PaO_2 than at rest (Nyman et al. 1995; Bernard et al. 1996). This is due to increased oxygen extraction by the muscles and increased cardiac output, which reduces capillary transit time in the pulmonary circulation and limits diffusion of oxygen (Funkquist et al. 1999; Roberts et al. 1999). This implies a lack of pulmonary adaptation in horses despite their athletic ability (Roberts et al. 1999). In the horse, the pulmonary artery is stiffer in caudodorsal regions of the lung and may be an adaptation to protect the vessel from high pressures during periods of intense exercise (Stack et al. 2014). However, this potentially alters the hypoxic pulmonary vasoconstrictive response to alveolar hypoxia leading to larger areas of VQ inequality. In contrast, ponies do not consistently become hypoxaemic during

exercise (Parks and Manohar 1983; 1984), suggesting that their ventilatory response is able to match their smaller metabolic demand (Katz et al. 1999) but may not make ponies any less susceptible to hypoxaemia during general anaesthesia. However, despite the development of arterial hypoxaemia, hypercapnia and hypertension during exercise, autoregulation of cerebral and cerebellar blood flow is maintained (Manohar & Goetz 1998). This suggests that the conscious horse is somewhat 'protected' against the effects of hypoxaemia, but the duration of intense exercise is usually short. This autoregulation of blood flow is attenuated during general anaesthesia with volatile anaesthetic agents, and with large concentrations of anaesthetic agent, autoregulation is abolished (Patel et al. 2015). In the face of arterial hypoxaemia, this will result in prolonged periods of neuronal hypoxia.

In summary, despite favourable anatomical and physiological adaptations, horses experience short periods of hypoxaemia during intense exercise. These adaptations become unfavourable during anaesthesia and recumbency, leading to large areas of alveolar atelectasis. This, in combination with non-gravitational influences and stiff vessels, result in preferential caudodorsal lung perfusion and will worsen VQ inequality. Consequently, there can be protracted periods of hypoxaemia during general anaesthesia, with loss of autoregulation of cerebral blood flow, which may increase the risk of anaesthesia associated mortality and morbidity.

Anaesthesia and Recumbency

Although arterial oxygenation is near ideal in conscious standing horses at rest, recumbency induces postural changes, which lead to impaired oxygenation, compounded by the respiratory depressant effects of general anaesthesia. It is widely accepted that anaesthetised horses and ponies, whether lying in lateral or dorsal

recumbency, will develop an increased [A-a]PO_2, which may lead to hypoxaemia (Hall et al. 1968; Mitchell & Littlejohn 1974; Steffey et al. 1977; Schatzmann et al. 1982; Rugh et al. 1984; Stegmann & Littlejohn 1987; Gleed & Dobson 1988; Nyman et al. 1988; Nyman et al. 1990; Steffey et al. 1990; Day et al. 1995). Dorsal recumbency, low pulse pressure, short procedures and emergent procedures were strong predictors of low (< 80 mmHg (10.7 kPa)) PaO_2 values, and male horses were more likely to become hypoxaemic (Whitehair & Willits 1999). Whilst the authors could not explain the male effect, they speculated that inspired oxygen fraction was lowest at the start of anaesthesia and hence, shorter procedures were more likely to lead an increased [A-a]PO_2. Round-bellied horses have a greater [A-a]PO_2 than their flat-bellied counterparts (Moens et al. 1995), and tall, light horses have improved oxygenation when compared with shorter and stockier animals (Mansel & Clutton 2008). Nevertheless, despite these potential associations, hypoxaemia does develop unpredictably in anaesthetised horses (Trim and Wan 1990) and further prospective investigations are necessary to identify definitive risk factors.

Although multifactorial, the hypoxaemia observed is mainly a result of ventilation perfusion (V_A/Q) inequality or 'mismatch' (Nyman & Hedenstierna 1989; Moens et al. 1998; Nyman et al. 2012; Grubb et al. 2014). Hypoventilation during anaesthesia does not generally lead to hypoxaemia due to the administration of oxygen enriched gas mixtures (West 2005), but will lead to varying degrees of hypercapnia (Moens 1989). The V_A/Q mismatch is largely due to atelectasis of dependent lung regions during recumbency (Nyman et al. 1990). Radiographic studies have shown that diffuse radiopaque densities develop in the dependent lung in laterally recumbent horses, 20 minutes following induction to general anaesthesia (McDonnell et al. 1979; Nyman et al. 1990). The radiographic densities that develop have been shown on necropsy to be

regions of atelectatic lung, which can be eliminated by large volume inflations (Nyman et al. 1990), in a manner similar to humans (Rothen et al. 1993; Rothen et al. 1999). These areas appear small when studied using CT, but comprise as much as 4 times the lung tissue as aerated regions (Reber et al. 1996). There are 3 mechanisms of atelectasis described - compression atelectasis occurs when the transmural pressure is reduced leading to alveolar collapse; absorption atelectasis which occurs when gas entering alveoli is less than that being absorbed into the blood; and loss of surfactant which will also result in atelectasis due to alteration in alveolar distension (Magnusson & Spahn 2003). In the horse however, compression atelectasis has been determined as the major cause, contributing up to 20% or 30% of total lung tissue in lateral and dorsal recumbency, respectively (Sorenson & Robinson 1980; Nyman & Hedenstierna 1989). Cranial displacement of the diaphragm occurs in the spontaneously breathing, anaesthetised horse (Benson et al. 1982), and functional residual capacity (FRC) is reduced by up to 50% when compared to the animal standing (McDonnell et al. 1979, Sorenson & Robinson 1980). The closing capacity of the lung may exceed FRC and lead to airway collapse (Sorenson & Robinson 1980). The atelectatic regions are larger than those in other species, and this is mirrored by greater gas exchange impairment, as determined by calculating shunt fraction (Nyman et al. 1990). Furthermore the magnitude of CT densities observed during general anaesthesia correlates well with the degree of shunt or venous admixture (Nyman et al. 1990). Predominantly, it is these areas of shunt, together with areas of lung with 'low' V_A/Q ratios, which contribute most significantly to the observed [A-a]PO_2 gradient. Areas of 'high' V_A/Q ratios, or alveolar deadspace, contribute little, since perfusion to these areas is poor.

Treatment of Hypoxaemia

Hypoxaemia during anaesthesia may be successfully treated, by using positive pressure ventilation (PPV) strategies, by increasing the inspired oxygen fraction, and by administering drugs or other gases. However, hypoxaemia in the recovery stall may be more problematic because it is not recognised or measured, is difficult to prevent and treat and is made worse by repeated attempts to stand.

1. Ventilatory Strategies

In the past it has been documented that PPV, administered from the outset of anaesthesia, can lead to improved arterial oxygenation (Hall et al. 1968; Moens 2013). However, detrimental effects of positive intra-thoracic pressure have long been known (Cournand et al. 1948; Hodgson et al. 1986; Mizuno et al. 1994; Raisis et al. 1995). Cardiac output is reduced due to reduced preload (compression of the vena cava and impedence to cardiac filling), and pulmonary perfusion falls (Hodgson et al. 1986). In isolated lung preparations, positive pressure has also been demonstrated to force blood to more dependent areas of non-ventilated lung (West et al. 1964), which may worsen shunt (Bindslev et al. 1981). Overall, this may lead to reductions in tissue oxygen delivery. Mechanical ventilation in itself can cause atelectasis as a result of alveolar damage and the mechanisms are varied: alveolar wall damage through the development of shear stresses, and the squeezing out of surfactant molecules from small alveoli by rhythmic compression and decompression of the alveolar lining (Lachmann 1992).

Techniques of differential lung ventilation have been described in order to manage reduced PaO_2 in anaesthetised horses. Both independent PPV of each lung and the application of PPV with positive end-expiratory pressure (PEEP) to dependent regions of lung (rather than whole lung) via tracheotomy, improve PaO_2 and reduces shunt fraction (Nyman et al. 1987; Nyman & Hedenstierna 1989; Moens et al. 1992; 1994),

Neither of these techniques are suitable for standard clinical use but add to evidence that atelectasis is the cause of the increased [A-a]PO_2 gradient observed.

The open lung concept (OLC) is used to prevent or treat hypoxaemia in the human and serves to 'open up the whole lung (with an alveolar recruitment manoeuvre) and keep it totally open, with the least influence on the cardiocirculatory system' (Lachmann 1992). The technique should maintain a shunt fraction of less than 10%, at the minimum intrathoracic pressure, to prevent adverse effects, such as alveolar trauma and cardiovascular depression (Papadakos & Lachmann 2007). A renewed interest in a variety of PPV strategies has coincided with the development of technologies, which enable the anaesthetist to easily provide PEEP or continuous positive airway pressure (CPAP) to large animals. However, pressures necessary for recruitment of atelectatic alveoli are high and not easily achievable in the horse. Furthermore, it is difficult to maintain this pressure for the period of time necessary to have a significant effect on PaO_2. Intermittent positive pressure ventilation (IPPV) with PEEP, without an initial alveolar recruitment manoeuvre, does not improve pulmonary function in horses anaesthetised for colic surgery (Pauritsch 1997). Therefore it is important that an initial recruitment manoeuvre is performed (Moens & Böhm 2011). A single hyperinflation of 50 cmH_2O for 50 seconds in anaesthetised horses provides only a small transient benefit in oxygenation (Santos et al. 2013). Applications of modified OLC (mOLC) techniques significantly improve PaO_2 in healthy horses (Bringewatt et al. 2010), horses anaesthetised for exploratory laparotomy (Hopster et al. 2011), and healthy ponies (Wettstein et al. 2006). In the study by Hopster et al. (2011), the recruitment had to be repeated multiple times, with some horses not responding as anticipated, but the improvement in PaO_2 persisted into recovery and recovery times were faster (but not of better quality). In the aforementioned investigations, MAP, cardiac output or both

decreased. Incremental titration of PEEP up to 20 cmH_2O significantly reduces cardiac output but does improve gas exchange (Ambrósio et al. 2013). As many of these studies involve clinical cases, anaesthetic techniques varied and some horses were supported with catecholamines making the exact effect of PPV on the cardiovascular system during general anaesthesia difficult to interpret. In one experimental study in anaesthetised healthy horses, cardiac output and blood pressure were significantly lower when mechanically ventilated, compared with those spontaneously breathing (Edner et al. 2005). In the latter study, muscle and skin perfusion were also adversely affected which may have implications postoperatively. Continuous positive airway pressure (CPAP) maintains positive airway pressure throughout the entire respiratory cycle during spontaneous breathing and serves to maintain functional residual capacity (FRC), prevent atelectasis and reduce shunt fraction (Cairo 2012). As intrathoracic pressures are lower than with other PPV techniques, cardiovascular function may be preserved. Anaesthetised horses supported with CPAP had significantly higher PaO_2 values compared to horses without support and there were no differences in dobutamine requirement between the 2 groups (Mosing et al. 2013). Although the deleterious effects of PPV may not occur in all horses, it is impossible to predict those which may tolerate these strategies. PEEP reduces atelectasis but may worsen the degree of shunt, presumably by forcing pulmonary blood down into dependent regions and increasing the blood supply to the atelectatic region (West et al. 1964; Swanson & Muir 1988), but it may also improve gas exchange by virtue of maintaining alveolar integrity (Hedenstierna & Lattuada 2002; Ambrósio et al. 2013). The improvement in arterial oxygenation appears to be disproportionate to the level of PEEP and seems to be more effective in patients with high levels of venous admixture (Hewlett et al. 1974) and therefore is probably applicable to anaesthetised, dorsally recumbent horses. Optimal

pressures and methods of recruitment which lead to benefits that outweigh the potential for harm, are questions yet to be answered and more controlled studies are essential to improve our understanding in this area. Additionally, it is likely that cardiovascular supportive drugs will be necessary when utilising these techniques to maintain tissue oxygen delivery.

2. Inspired Oxygen Fraction

The administration of approximately 100% oxygen (FiO_2 1.0), can potentially contribute to V_A/Q inequality by exacerbating alveolar collapse (absorption atelectasis) (Rothen et al. 1995). Normal PaO_2 can be achieved in humans during routine anaesthesia with a FiO_2 of 0.3 – 0.35 (Nunn 1964). If one assumes normal arterial PCO_2, haemoglobin and arterial-mixed venous oxygen content difference, the PaO_2 is largely determined by the inspired oxygen fraction and venous admixture (Lumb & Pearl 2010). At higher levels of venous admixture (higher shunt fraction), increasing the FiO_2 has very little effect on the PaO_2 (Benator et al. 1973). This goes some way to explain why PaO_2 values do not rise appreciably when FiO_2 is increased in some dorsally recumbent horses and is suggestive that these animals have large areas of atelectasis and shunt. Alveoli ventilated with air remain open for 8 – 9 hours, whereas those ventilated with 100% oxygen collapse within 8 minutes (Joyce et al. 1993). Recruited alveoli de-recruit within 5 minutes if the FiO_2 is 1.0 compared with 40 minutes if the FiO_2 is 0.4 (Rothen et al. 1995). Furthermore, minute ventilation of horses increases as FiO_2 is reduced (Pelletier & Leith 1995). Anaesthetised horses breathing high oxygen concentrations (FiO_2 > 0.85) hypoventilate more and have increased atelectasis and shunt fraction than those breathing lower FiO_2 of 0.21 - 0.3 (Cuvelliez et al. 1990; Marntell et al. 2005). Adequate PaO_2 values were achieved in anaesthetised horses in lateral recumbency breathing a variety of FiO_2 values (0.25 –

0.9) by mixing oxygen with helium (Staffieri et al. 2009). Further work using this technique in dorsally recumbent horses is warranted since this position affects pulmonary function more. Notably, reducing the FiO_2 from > 0.95 to 0.5 during anaesthesia does not appear to change shunt fraction in dorsally recumbent, mechanically ventilated horses (Hubbell et al. 2011), so decreasing FiO_2 partway through anaesthesia does not offer advantages.

Breathing of oxygen enriched gas mixtures can lead to the production of ROS, which disrupt the activity of nitric oxide (NO), an endogenous pulmonary vasodilator, enhance vasoconstrictive mediators, and cause an increase in pulmonary vascular pressure (Mills & Higgins 1997). These ROS can also directly damage lung tissue by provoking an inflammatory response when antioxidants are overwhelmed, and pulmonary epithelial cells are particularly susceptible to oxidant injury (Mills and Higgins 1997). ROS have also been shown to inhibit receptor-dependent production of NO in the canine coronary endothelium (Seccombe et al. 1994). However, ROS-induced damage has not been demonstrable in anesthetised horses (Portier et al. 1999), but further work in this area is warranted. When anaesthetising horses it is prudent then to begin at lower FiO_2 values (0.3) whilst monitoring PaO_2, to encourage adequate spontaneous ventilation and limit the development of ROS. Identification of hypoxaemia should be treated initially by altering the FiO_2. As compression atelectasis is the predominant cause of abnormal gas exchange in the horse rather than absorption atelectasis (Sorenson & Robinson 1980; Nyman & Hedenstierna 1989), steadily increasing FiO_2 may not improve matters greatly (Benator et al. 1973) and other treatment may be necessary.

3. Drug Therapy

The β_2 adrenergic agonists, clenbuterol and salbutamol (albuterol), have been administered to anaesthetised horses in an attempt to improve arterial oxygenation. Due

to the limited number of studies, and conflicting results, clenbuterol is not recommended as the response appears to be unpredictable. Intravenous administration of clenbuterol can improve PaO_2 (Keegan et al. 1991), worsen it (Dodam et al. 1993), or effect no change (Lee et al. 1998). It can result in an increase of heart rate and oxygen consumption, and lead to profuse sweating (Keegan et al. 1991; Dodam et al. 1993). An increase in heart rate in the face of hypoxaemia may result in myocardial hypoxia due to increased oxygen demand.

Salbutamol is administered to horses using a metered dose inhaler. When given to horses with PaO_2 values less than 70 mmHg (9.3 kPa), PaO_2 increases significantly and sweating is observed (Robertson & Bailey 2002). In a later investigation, in addition to increased PaO_2, heart rate and cardiac output increased after salbutamol administration, prompting speculation that pulmonary perfusion was altered rather than ventilation (Patschova et al. 2010). However, adverse cardiovascular events (sinus and ventricular tachycardia and hypotension), suggestive of a significant systemic effect, with no improvement in PaO_2 have also been described (Casoni et al. 2014). Currently, in equine anaesthesia, inhaled salbutamol is administered relatively commonly to treat hypoxaemia and clinical experience would suggest it is beneficial in many cases. Nevertheless, further investigations are required to determine its actual mechanism of action, optimal dose, repeatability and incidence of adverse effects.

4. Nitric Oxide (NO)

In 1987, Palmer et al. described the relaxant effect of NO on the vascular endothelium, and a variety of systemically administered vasodilators are known to have their therapeutic effect by causing the release of nitric oxide in order to mimic its effect (Frostell et al. 1991). However, this systemic administration causes generalised

vasodilation resulting in peripheral hypotension (Frostell et al. 1991), and are therefore unsuitable for selective pulmonary vasodilation.

The therapeutic use of inhaled nitric oxide gas (iNO) results in selective pulmonary vasodilation (Gerlach et al. 1993; Nyman et al. 2012). Administration of iNO to conscious lambs reversed hypoxic pulmonary vasoconstriction without systemic effects (Frostell et al. 1991), and reduced pulmonary arterial pressure to improve VQ matching in neonatal pigs (Nelin et al. 1994). Nitric oxide is used in ARDS in humans to selectively improve the perfusion of ventilated regions of lung and reduce intrapulmonary shunting (Bigatello et al. 1994), and iNO during one lung ventilation diverts blood away from the hypoxic lung (Hambraeus-Jonzon et al. 1998).

The effects of iNO are restricted to the pulmonary circulation because excess NO binds tightly to oxyhaemoglobin and is rapidly removed from the alveolus by the formation of methaemoglobin and nitrite (Wennmalm et al. 1993). However, high doses of iNO can lead to lethal methaemoglobinaemia and pulmonary oedema (Gerlach et al. 1993). Excess NO in the breathing circuit, or recirculation of exhaled NO, readily combines with oxygen to form nitrogen dioxide (NO_2). Pulmonary injury occurs in a dose-dependent manner when even low concentrations of NO_2 are inhaled, and may result in diffuse injury and oedema (Elsayed 1994). If iNO is given as a pulse (PiNO) early in inspiration it is almost completely absorbed (92%) and does not appear to build up within the breathing circuit (Heinonen et al. 2000). Furthermore, toxicity from iNO can be eliminated if the dose administered is below 30 ppm, and the National Institute for Occupational Safety and Health has set a time-weighted average NO value of 25 ppm.

The administration of iNO to humans with severe acute ARDS produces conflicting results, with some studies showing little effect at all (Rossaint et al. 1995; Brett et al. 1998), or even reductions in arterial oxygenation (Barberà et al. 1996). If iNO is

administered (10 ppm constantly for 20 minutes) to anaesthetised spontaneously breathing horses, venous admixture (shunt fraction or $\dot{Q}_s/\ \dot{Q}_t$) does not change significantly (Young et al. 1999). However, the administration of PiNO in the first half of inspiration, to anaesthetised horses during both spontaneous and controlled ventilation improves $\dot{Q}_s/\ \dot{Q}_t$ (Heinonen et al. 2001; 2002) and, when given in the first 30 – 43% of inspiration, the largest peak in PaO_2 occurs and reduces $\dot{Q}_s/\ \dot{Q}_t$ from 32 to 25% (Nyman et al. 2012). If delivery of PiNO is delayed and delivered during the second half of inspiration the effect is lost (Heinonen et al. 2002). Longer duration (or continuous delivery) and later pulses, deliver NO to boundary regions, which lie between the ventilated and atelectatic areas and counteracts hypoxic pulmonary vasoconstriction, increasing $\dot{Q}_s/\ \dot{Q}_t$ (Heinonen et al. 2000). The effect of PiNO does persist into the recovery period following 2.5 hours of treatment (Grubb et al. 2008), which was in contrast to earlier work (Heinonen et al. 2001). This information is pertinent as hypoxaemia has been identified in recumbent horses recovering from general anaesthesia (Mason et al. 1987; McMurphy & Cribb 1989), and therefore some persistence of the effect of PiNO is very useful. One major concern with PiNO therapy is a rebound increase in endogenously released endothelin-1 (ET-1), a pulmonary vasoconstrictor, which would reverse the beneficial effects of PiNO by reducing pulmonary perfusion. Hypoxaemia increases the secretion of ET-1 (Cargill et al. 1995) and therefore we can speculate that alleviation of hypoxaemia by administering PiNO reduces ET-1 concentrations although this has yet to be conclusively proven (Grubb et al. 2013a). No increase in ET-1 concentrations has been found in horses receiving PiNO (Grubb et al. 2008; 2013a; 2013b). The improvements in PaO_2 and $\dot{Q}_s/\ \dot{Q}_t$ as a result of PiNO administration occur because of ‘en masse’ movement of blood against gravity from dependent, and presumably atelectatic lung, to non-dependent, ventilated lung

(Grubb et al. 2014). This study was limited by the small number of animals due to the complexity of the experimental technique and further work is necessary to demonstrate this conclusively. Refinement of the PiNO technique must ensure the smallest concentration of NO possible is delivered to the horse, that the NO is delivered to the correct alveoli, and that NO_2 does not build up in the rebreathing circuit. More information is required before the technique can be adopted into clinical practice. As the equipment essential to deliver NO in this way to anaesthetised horses is specialised and prototypical, currently it remains unsuitable for clinical application. Nevertheless, manipulation of pulmonary perfusion in this way appears to be an attractive therapeutic intervention.

Conclusion

The mortality and morbidity associated with general anaesthesia in the horse remains unacceptably high. Whilst the horse has favourable anatomical and physiological adaptations for athletic exercise, these become unfavourable during recumbency induced by anaesthesia. Although we know, or at least can surmise, why horses die as a result of anaesthesia, we cannot always prevent these circumstances from occurring. Hypoxaemia is a common complication in the anaesthetised horse, which is easy to recognise but very challenging to treat. There have been many attempts at improving V_A/Q matching in the hope of alleviating the severity of hypoxemia. Many of these interventions target ventilation and can be associated with unpredictable adverse effects, Alternative treatment methods aim to change perfusion instead. Before any of the techniques described in this review can be accepted into widespread clinical use, additional evidence is necessary to demonstrate consistent beneficial effects and to ascertain their influence on the survival of horses undergoing general anaesthesia.

References

Allen DG & Orchard CH (1987) Myocardial contractile function during ischemia and hypoxia. Circ Res, 60, 153 – 168.

Ambrósio AM, Ida KK, Souto MTMR, Oshiro AH, Fantoni D (2013) Effects of positive end-expiratory pressure titration on gas exchange, respiratory mechanics and hemodynamics in anesthetized horses. Vet Anaesth Analg, 40, 564 – 572.

499 Barberà JA, Roger N, Roca J, Rodriguez-Roisin R, Rovira I, Higenbottam TW (1996)
500 Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic
501 obstructive pulmonary disease. Lancet, 347, 436 – 440.
502 Benator SR, Hewlett AM, Nunn JF. (1973) The use of iso-shunt lines for control of
503 oxygen therapy. Br J Anaesth, 45, 711 – 718.
504 Benson GJ, Kneller SK, Manohar M, Thurmon JC (1982) Radiographic characterization
505 of diaphragmatic excursion in halothane-anesthetized ponies: Effect of mode of
506 ventilation and muscle paralysis. Equine Vet Sci, 2, 90 – 94.
507 Bernard C [1865] 1957 Introduction á l'étude de la médecine expérimentale (An
508 Introduction to the Study of Experimental Medicine). Reprint: Greene HC, Dover, New
509 York.
510 Bernard SL, Glenny RW, Erickson HH, Fedde MR, Polissar N, Basaraba RJ, Hlastala
511 MP (1996) Minimal redistribution of pulmonary blood flow with exercixe in racehorses.
512 J Apply Physiol, 81, 1062 – 1070.
513 Bidwell LA, Bramlage LR, Rood WA (2007) Equine perioperative fatalities associated
514 with general anaesthesia at a private practice – a retrospective case series. Vet Anaesth
515 Analg, 34 (1), 23 – 30.
516 Bigatello LM, Hurford WE, Kacmarek RM, Roberts JD, Zapol WM (1994) Prolonged
517 inhalation of low concentrations of nitric oxide in patients with severe adult respiratory
518 distress syndrome: effects on pulmonary hemodynamics and oxygenation. Anesthesiol,
519 80, 761 – 770.
520 Bindslev L, Hedenstierna G, Santesson J, Gottlieb I, Carvallhas A (1981) Ventilation-
521 perfusion distribution during inhalation anaesthesia. Acta Anaesth Scand, 25, 360 – 371.
522 Brett SJ, Hansell DM, Evans TW (1998) Clinical correlates in acute lung injury
523 response to inhaled nitric oxide. Chest, 114, 1397 – 1404.

524 Bringewatt T, Hopster K, Kästner SBR, Rohn K, Ohnesorge B (2010) Influence of
525 modified open lung concept ventilation on the cardiovascular and pulmonary function
526 of horses during total intravenous anaesthesia. Vet Rec, 167, 1002 – 1006.
527 Cairo JM (2012) Pilbeam's Mechanical Ventilation: Physiological and Clinical
528 Applications (5th ed), Elsevier, Missouri, US.
529 Cargill RI, Kiely DG, Clark RA, Lipworth BJ (1995) Hypoxaemia and release of
530 endothelin-1. Thorax, 50, 1308 – 1310.
531 Casoni D, Spadavecchia C, Adami C (2014) Cardiovascular changes after
532 administration of aerosolized salbutamol in horses: five cases. Acta Vet Scand, 56: 49.
533 Clerbaux T, Gustin P, Detry B, Cao ML, Frans A (1993) Comparative study of the
534 oxyhaemoglobin dissociation curve of four mammals: Man, dog, horse and cattle.
535 Comp Biochem Physiol, 106A (4), 687 – 694.
536 Costa-Farré C, Prades M, Ribera T, Valero O, Taurà P (2014) Does intraoperative low
537 arterial partial pressure of oxygen increase the risk of surgical site infection following
538 emergency exploratory laparotomy in horses? The Vet J, 200 (1), 175 – 180.
539 Cournand A, Motley HL, Werko L, Richards DW (1948) Physiological studies of the
540 effects of intermittent positive pressure breathing on cardiac output in man. Am J
541 Physiol, 152, 162- 174.
542 Cuvelliez SG, Eicker SW, McLauchlan C, Brunson DB (1990) Cardiovascular and
543 respiratory effects of inspired oxygen fraction in halothane-anesthetized horses. Am J
544 Vet Res, 51 (8), 1226 – 1231.
545 Day TK, Gaynor JS, Muir WW, Bednarski RM, Mason DE (1995) Blood gas values
546 during intermittent positive pressure ventilation and spontaneous ventilation in 160
547 anesthetized horses positioned in lateral or dorsal recumbency. Vet Surg, 26, 266 – 276.

548 Dodam JR, Moon RE, Olson NC, Exposito AJ, Fawcett TA, Huang YC, Theil DR,
549 Camporesi E, Swanson CR (1993) Effects of clenbuterol hydrochloride on pulmonary
550 gas exchange and hemodynamics in anesthetized horses. Am J Vet Res, 54 (5), 776 –
551 782.
552 Dugdale AHA, Obhrai J, Cripps PJ (2016) Twenty years later: a single-centre, repeat
553 retrospective analysis of equine perioperative mortality and investigation of recovery
554 quality. Vet Anaesth Analg, 43 (2), 171 – 178.
555 Edner A, Nyman G, Essén-Gustavsson B (2005) The effects of spontaneous and
556 mechanical ventilation on central cardiovascular function and peripheral perfusion
557 during isoflurane anaesthesia in horses. Vet Anaesth Analg, 32, 136 – 146.
558 Elsayad NM (1994) Toxicity of nitrogen dioxide: an introduction. Toxicology, 89, 161
559 – 174.
560 Frostell C, Fratacci M, Wain JC, Jones R, Zapol WM (1991) A selective pulmonary
561 vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation, 83, 2038 –
562 2047.
563 Funkquist P, Wagner PD, Hedenstierna G, Persson SGB, Nyman G (1999) Ventilation-
564 perfusion relationships during exercise in Standardbred trotters with red cell
565 hypervolaemia. Eq Vet J Suppl, 30, 107 – 113.
566 Gerlach H, Pappert D, Lewandowski K, Rossaint R, Falke KJ (1993) Long-term
567 inhalation with evaluated low doses of nitric oxide for selective improvement of
568 oxygenation in patients with acute respiratory distress syndrome. Int Care Med, 19, 443
569 – 449.
570 Gleed RD & Dobson A (1988) Improvement in arterial oxygen tension with change in
571 posture in anaesthetized horses. Res Vet Sci, 44, 255 – 259.
572 Gottrup F (2004) Oxygen in wound healing and infection. World J Surg, 28, 312 – 315.

Grubb TL, Högman M, Edner A, Frendin JHM, Heinonen E, Malavasi LM, Frostell CG, Rýden A, Alving K, Nyman G (2008) Physiologic responses and plasma endothelin-1 concentrations associated with abrupt cessation of nitric oxide inhalation in isoflurane-anesthetized horses. Am J Vet Res, 69 (3), 423 – 430.

Grubb T, Edner A, Frendin JHM, Funkquist P, Rýden A, Nyman G (2013a) Oxygenation and plasma endothelin-1 concentrations in healthy horses recovering from isoflurane anaesthesia administered with or without pulse-delivered inhaled nitric oxide. Vet Anaesth Analg, 40, e9 – e18.

Grubb T, Frendin JHM, Edner A, Funkquist P, Hedenstierna G, Nyman G (2013b) The effects of pulse-delivered inhaled nitric oxide on arterial oxygenation, ventilation-perfusion distribution and plasma endothelin-1 concentration in laterally recumbent isoflurane-anaesthetized horses. Vet Anaesth Analg, 40, e19 – e30.

Grubb TL, Lord PF, Berger M, Larsson C, Rýden A, Frendin J, Funkquist P, Edner A, Nyman G (2014) Effects of pulse-delivered inhaled nitric oxide administration on pulmonary perfusion and arterial oxygenation in dorsally recumbent isoflurane-anesthetized horses. Am J Vet Res, 75 (11), 949 – 955.

Grubbström J, Berglund B, Kaijser L (1993) Myocardial oxygen supply and lactate metabolism during marked arterial hypoxaemia. Acta Physiol Scand, 149, 303 – 310.

Hall LW, Gillespie JR, Tyler WS (1968) Alveolar - arterial oxygen tension differences in anaesthetised horses. Br J Anaesth, 40, 560 – 568.

Hambraeus-Jonzon K, Bindslev L, Frostell C, Hedenstierna G (1998) Individual lung blood flow during unilateral hypoxia: effects of inhaled nitric oxide. Eur Respir J, 11, 565 – 570.

Hedenstierna G & Lattuada M (2002) Gas exchange in the ventilated patient. Curr Opin Crit Care, 8, 39 – 44.

598 Hedenstierna G, Nyman G, Frostell C (2005) Animal models of lung physiology during
599 anesthesia. In: Handbook of Laboratory Animal Science – Volume III: Animal Models
600 (2nd ed). Hau J & Van Hoosier Jr GL (eds), CRC Press, Florida, US, 263 – 288.
601 Heinonen E, Högman M, Meriläinen P (2000) Theoretical and experimental comparison
602 of constant inspired concentration and pulsed delivery in NO therapy. Int Care Med,
603 26, 1116 – 1123.
604 Heinonen E, Hedenstierna G, Meriläinen P (2001) Pulsed delivery of nitric oxide
605 counteracts hypoxaemia in the anaesthetised horse. Vet Anaesth Analg, 28, 3 – 11.
606 Heinonen E, Nyman G, Meriläinen P, Högman M (2002) Effect of different pulses of
607 nitric oxide on venous admixture in the anaesthetized horse. Br J Anaesth, 88 (3), 394 –
608 398.
609 Hewlett AM, Hulands GH, Nunn JF, Milledge JS (1974) Functional residual capacity
610 during anaesthesia III: Artificial ventilation. Br J Anaesth, 46, 495 – 503.
611 Hodgson DS, Steffey EP, Grandy JL, Woliner MJ (1986) Effects of spontaneous,
612 assisted and controlled ventilatory modes in halothane-anesthetized geldings. Am J Vet
613 Res, 47 (5), 992 - 996.
614 Hopkins RO & Bigler ED (2001) Pulmonary Disorders. In: Medical Neuropsychology
615 (2nd ed.) Tarter RE, Butters M, Beers SR (eds.). Kluwer Academic, New York, US, 25 –
616 50.
617 Hopster K, Kästner SBR, Rohn K, Ohnesorge B (2011) Intermittent positive pressure
618 ventilation with constant positive end-expiratory pressure and alveolar recruitment
619 manoeuvre during inhalation anaesthesia in horses undergoing surgery for colic, and its
620 influence on the early recovery period. Vet Anaesth Analg, 38, 169 – 177.

621 Hubbell JAE, Aarnes TK, Bednarski RM, Lerche P, Muir WW (2011) Effect of 50%
622 and maximal inspired oxygen concentrations on respiratory variables in isoflurane-
623 anesthetized horses. BMC Veterinary Research, 7 (23), doi:10.1186/1746-6148-7-23.
624 Johnston GM, Eastment JK, Wood JLN, Taylor PM (2002) The confidential enquiry
625 into perioperative equine fatalities (CEPEF): mortality results of Phases 1 and 2. Vet
626 Anaesth Analg, 29, 159-170.
627 Joyce CJ, Baker AB, Kennedy FR (1993) Gas uptake from unventilated areas of lung:
628 computer model of absorption atelectasis. J Appl Physiol, 74, 1107 – 1116.
629 Katz LM, Bayly WM, Hines MT, Sides RH (1999) Differences in the ventilatory
630 responses of horses and ponies to exercise of varying intensities. Equine Vet J Suppl,
631 30, 49 – 51.
632 Keegan D, Gleed RD, Sanders EA, Seaman GC, Wertz EM, Short CE (1991) Treatment
633 of low arterial oxygen tension in anesthetized horses with clenbuterol. Vet Surg, 20 (2),
634 148 – 152.
635 Lachmann B (1992) Open up the lung and keep it open. Intensive Care Med, 18, 319 –
636 321.
637 Lee YHL, Clarke KW, Alibhai HLK (1998) The cardiopulmonary effects of clenbuterol
638 when administered to dorsally recumbent halothane-anaesthetised ponies – failure to
639 increase arterial oxygenation. Res Vet Sci, 65, 227 – 232.
640 Lumb AB & Pearl RG (2010) Distribution of pulmonary ventilation and perfusion. In:
641 Nunn's Applied Respiratory Physiology (7^{th} ed.). Elsevier, Oxford, UK, 119 – 144.
642 Lundberg JON & Weitzberg E (1999) Nasal nitric oxide in man. Thorax, 54, 947 – 952.
643 Magnusson L & Spahn DR (2003) New concepts of atelectasis during general
644 anaesthesia. Br J Anaesth, 91 (1), 61 – 72.

645 Manohar M & Goetz TE (1998) Regional distribution of blood flow in the brain of
646 horses at rest and during exercise. Am J Vet Res, 59 (7), 893 – 897.
647 Mansell JC & Clutton RE (2008) The influence of body mass and thoracic dimensions
648 on arterial oxygenation in anaesthetized horses and ponies. Vet Anaesth Analg, 35, 392
649 – 399.
650 Marntell S, Nyman G, Hedenstierna G (2005) High inspired oxygen concentrations
651 increase intrapulmonary shunt in anaesthetised horses. Vet Anaesth Analg, 32, 338 –
652 347.
653 Mason DE, Muir WW, Wade A (1987) Arterial blood gas tensions in the horse during
654 recovery from general anesthesia. J Am Vet Med Assoc, 190 (8), 989, 994.
655 McDonnell WN, Hall LW, Jeffcott LB (1979) Radiographic evidence of impaired
656 pulmonary function in laterally recumbent anaesthetized horses. Equine Vet J, 11, 24 –
657 32.
658 McMurphy RM & Cribb PH (1989) Alleviation of postanesthetic hypoxemia in the
659 horse. Can Vet J, 30, 37 – 41.
660 Mills PC & Higgins AJ (1997) Oxidant injury, nitric oxide and pulmonary vascular
661 function: Implications for the exercising horse. Vet J, 153, 125 – 148.
662 Mitchell B & Littlejohn A (1974) The effect of anaesthesia and posture on the exchange
663 of respiratory gases and on the heart rate. Equine Vet J, 6 (4), 177 – 178.
664 Mizuno Y, Aida H, Hara H, Fujinaga T (1994) Cardiovascular effects of intermittent
665 positive pressure ventilation in the anesthetized horse. J Vet Med Sci, 56 (1), 39 -44.
666 Moens Y (1989) Arterial-alveolar carbon dioxide tension difference and alveolar dead
667 space in halothane-anaesthetised horses. Equine Vet J, 21, 282–284.
668 Moens Y, Gootjes P, Lagerweij E (1992) A tracheal tube-in-tube technique for
669 functional separation of the lungs in the horse. Eq Vet J, 24 (2), 103 – 106.

670 Moens Y, Lagerweij E, Gootjes P, Poortman J (1994) Differential artificial ventilation
671 in anesthetized horses positioned in lateral recumbency. Am J Vet Res, 55 (9), 1319 –
672 1326.
673 Moens Y, Lagerweij E, Gootjes P, Poortman J (1995) Distribution of inspired gas to
674 each lung in the anaesthetised horse and the influence of body shape. Equine Vet J, 27
675 (2), 110 – 116.
676 Moens Y, Lagerweij E, Gootjes P, Poortman J (1998) Influence of tidal volume and
677 positive end-expiratory pressure on inspiratory gas distribution and gas exchange during
678 mechanical ventilation in horses positioned in lateral recumbency. Am J Vet Res, 59
679 (3), 307 – 312.
680 Moens Y & Böhm S (2011) Ventilating horses: moving away from old paradigms. Vet
681 Anaesth Analg, 38, 165 – 168.
682 Moens Y (2013) Mechanical ventilation and respiratory mechanics during equine
683 anesthesia. Vet Clin Equine, 29, 51 – 67.
684 Mosing M, Rysnik M, Bardell D, Cripps PJ, MacFarlane P (2013) Use of continuous
685 positive airway pressure (CPAP) to optimise oxygenation in anaesthetised horses – a
686 clinical study. Eq Vet J, 45, 414 – 418.
687 Nelin LD, Moshin J, Thomas CJ, Sasidharan P, Dawson CA (1994) The effect of
688 inhaled nitric oxide on the pulmonary circulation of the neonatal pig. Pediat Res, 35, 20
689 – 24.
690 Nitric oxide (1994) Centers for disease control and prevention, U.S. Department of
691 Health & Human Services. Available at: http://www.cdc.gov/niosh/idlh/10102439.html
692 [Accessed: 9th March 2016]
693 Nunn JF (1964) Factors influencing the arterial oxygen tension during halothane
694 anaesthesia with spontaneous respiration. Br J Anaesth, 36, 327 – 341.

695 Nyman G, Frostell C, Hedenstierna G, Funkquist B, Kvart C, Blomqvist H (1987)
696 Selective mechanical ventilation of dependent lung regions in the anaesthetized horse in
697 dorsal recumbency. Br J Anaesth, 59, 1027 – 1034.
698 Nyman G, Funkquist B, Kvart C (1988) Postural effects on blood gas tension, blood
699 pressure, heart rate, ECG and respiratory rate during prolonged anesthesia in the horse. J
700 Vet Med Assoc, 35, 54 – 62.
701 Nyman G & Hedenstierna G (1989) Ventilation-perfusion relationships in the
702 anaesthetised horse. Equine Vet J, 21 (4), 274 – 281.
703 Nyman G, Funkquist B, Kvart C, Frostell C, Tokics L, Strandberg Å, Lundquist H,
704 Lundh B, Brismar B, Hedenstierna G (1990) Atelectasis causes gas exchange
705 impairment in the anaesthetised horse. Eq Vet J, 22 (5), 317 – 324.
706 Nyman G, Björk M, Funkquist P, Persson GB, Wagner PD (1995) Ventilation-perfusion
707 relationships during graded exercise in the Standardbred trotter. Eq Vet J Suppl 18, 63 –
708 69.
709 Nyman G, Grubb TL, Heinonen E, Frendin J, Edner A, Malavasi LM, Frostell C,
710 Högman M (2012) Pulsed delivery of inhaled nitric oxide counteracts hypoxaemia
711 during 2.5 hours of inhalation anaesthesia in dorsally recumbent horses. Vet Anaesth
712 Analg, 39, 480 – 487.
713 Palmer RMJ, Ferrige AG, Moncada SA (1987) Nitric oxide release accounts for the
714 biological activity of endothelium-derived relaxing factor. Nature, 327, 524 – 526.
715 Papadakos PJ & Lachmann B (2007) The open lung concept of mechanical ventilation:
716 The role of recruitment and stabilization. Critical Care Clinics, 23 (2), 241 – 250.
717 Parks CM & Manohar M (1983) Distribution of blood flow during moderate and
718 strenuous exercise in ponies (Equus caballus). Am J Vet Res, 44, 1861 – 1866.

719 Parks CM & Manohar M (1984) Blood-gas tensions and acid-base status in ponies
720 during treadmill exercise. Am J Vet Res, 45, 15 – 19.
721 Pascoe PJ, McDonell, WN, Trim CM, Van Gorder J (1983) Mortality rates and
722 associated factors in equine colic operations – a retrospective study of 341 operations.
723 Can Vet J, 24, 76 – 85.
724 Patel PM, Drummond JC, Lemkuil BP (2015) Cerebral physiology and the effects of
725 anesthetic drugs. In: Miller's Anesthesia (8th ed), Cohen NH, Eriksson LI, Fleisher LA,
726 Winer-Kronish JP, Young WL (eds) Elsevier Saunders, Philadelphia, US, 387 – 422.
727 Patschova M, Kabes R, Krisova S (2010) The effects of inhalation salbutamol
728 administration on systemic and pulmonary hemodynamic, pulmonary mechanics and
729 oxygen balance during general anaesthesia in the horse. Vet Med, 55, 445 – 456.
730 Pauritsch K (1997) Positive end-expiratory pressure ventilation in combination with
731 end-inspiratory breath-holding during anaesthesia in colic horses. DVM dissertation,
732 Equine Clinic, University of Hannover.
733 Pelletier N & Leith DE (1995) Ventilation and carbon dioxide exchange in exercising
734 horses: effect of inspired oxygen fraction. J Appl Physiol, 78 (2), 654 – 662.
735 Pelletier N, Robinson NE, Kaiser L, Derksen FJ, (1998) Regional differences in
736 endothelial function in horse lungs: possible role in blood flow distribution. J Appl
737 Physiol, 85 (2), 537 – 542.
738 Portier K, Crouzier D, Guichardant M, Prost M, Debouzy J, Kirschvink N, Fellmann N,
739 Lekeux P, Coudert J (2009) Effects of high and low inspired fractions of oxygen on
740 horse erythrocyte membrane properties, blood viscosity and muscle oxygenation during
741 anaesthesia. Vet Anaesth Analg, 36 (4), 287 – 298.

742 Raisis AL, Blissitt KJ, Henley W, Rogers K, Adams V, Young LE (1995) The effects of
743 halothane and isoflurane on cardiovascular function in laterally recumbent horses. Br J
744 Anaesth, 95 (3), 317 – 325.
745 Reber A, Engberg G, Sporre B, Kviele L, Rother H-U, Wegenius G, Nylind U,
746 Hedenstierna G (1996) Volumetric analysis of aeration in the lungs during general
747 anaesthesia. Br J Anaesth, 76, 760 – 766.
748 Roberts CA, Marlin DJ, Lekeux P (1999) The effects of training on ventilation and
749 blood gases in exercising Thoroughbreds. Equine Vet J Suppl, 30, 57 – 61.
750 Robertson SA & Bailey JE (2002) Aerosolized salbutamol (albuterol) improves PaO_2 in
751 hypoxaemic anaesthetized horses – a prospective clinical trial in 81 horses. Vet Anaes
752 Analg, 29, 212 – 218.
753 Romer LM, Dempsey JA, Lovering A, Eldridge M (2006) Exercise-induced arterial
754 hypoxemia: Consequences for locomotor muscle fatigue. Advances in Exp Med Biol,
755 588, 47 – 55.
756 Rossaint R, Gerlach H, Schmidt-Ruhnke H, Pappert D, Lewandowski K, Steudel W,
757 Falke K (1995) Efficacy of inhaled nitric oxide in patients with severe ARDS. Chest,
758 107, 1107 – 1115.
759 Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G (1993) Re-expansion
760 of atelectasis during general anaesthesia: a computed tomography study. Br J Anaesth,
761 71, 788 – 795.
762 Rothen HU, Sporre B, Engberg G, Wegenius G, Reber A, Hedenstierna G (1995)
763 Prevention of atelectasis during general anaesthesia. Lancet, 345, 1387 – 1391.
764 Rothen HU, Neumann P, Berglund JE, Valtysson J, Magnusson A, Hedenstierna G
765 (1999) Dynamics of re-expansion of atelectasis during general anaesthesia. Br J
766 Anaesth, 82 (4), 551 – 556.

767 Rugh KS, Garner HE, Hatfield DG, Herrold D (1984) Arterial oxygen and carbon
768 dioxide tensions in conscious laterally recumbent ponies. Eq Vet J, 16 (3), 185 – 188.
769 Santos M, Ibancovichi JA, Lopez-Sanroman FJ, Tendillo FJ (2013) Effects of single
770 hyperinflation using a sustained high pressure manoeuvre during inhalation anaesthesia
771 in horses. Vet J, 197, 892 – 895.
772 Schatzmann U, Koehli M, Dudan F, Rohr W, Jones RS (1982) Effect of postural
773 changes on certain circulatory and respiratory values in the horse. Am J Vet Res, 43,
774 1003 – 1005.
775 Seccombe JF, Pearson PJ, Schaff HV (1994) Oxygen radical-mediated vascular injury
776 selectively inhibits receptor-dependent release of nitric oxide from canine coronary
777 arteries. J Thorac Cardiovasc Surgery, 107, 505 – 509.
778 Sorenson PR & Robinson NE (1980) Postural effects on lung volumes and
779 asynchronous ventilation in anaesthetized horses. J Appl Physiol, 48, 97 – 103.
780 Stack A, Derksen FJ. Williams KJ, Robinson NE, Jackson WF (2014) Lung region and
781 racing affect mechanical properties of equine pulmonary microvasculature. J Appl
782 Physiol, 117, 370 – 376.
783 Staffieri F, Bauquier SH, Moate PJ, Driessen B (2009) Pulmonary gas exchange in
784 anaesthetised horses mechanically ventilated with oxygen or a helium/oxygen mixture.
785 Eq Vet J, 41 (8), 747 - 752
786 Steffey EP, Wheat JD, Meagher DM, Norrie RD, McKee J, Brown M, Arnold J (1977)
787 Body position and mode of ventilation influences arterial pH, oxygen, and carbon
788 dioxide tensions in halothane-anesthetized horses. Am J Vet Res, 38 (3), 379 – 382.
789 Steffey EP, Kelly AB, Hodgson DS, Grandy JL, Woliner MJ, Willits N (1990) Effects
790 of body posture on cardiopulmonary function in horses during five hours of constant-
791 dose halothane anesthesia. Am J Vet Res, 51 (1), 11 – 16.

792 Steffey EP, Willits N, Woliner M (1992) Hemodynamic and respiratory responses to
793 variable arterial partial pressure of oxygen in halothane-anesthetized horses during
794 spontaneous and controlled ventilation. Am J Vet Res, 53 (10), 1850 – 1858.
795 Stegmann GF & Littlejohn A (1987) The effect of lateral and dorsal recumbency on
796 cardiopulmonary function in the anaesthetised horse. J S Afr Vet Assoc, 58 (1), 21 – 27.
797 Swanson CR & Muir WW (1988) Hemodynamic and respiratory responses in
798 halothane-anesthetized horses exposed to positive end-expiratory pressure alone and
799 with dobutamine. Am J Vet Res, 49 (4), 539 – 542.
800 Trim CM & Wan PY (1990) Hypoxaemia during anaesthesia in seven horses with colic.
801 J Ass Vet Anaesth, 17, 45 – 49.
802 Turner CE, Barker-Collo SL, Connell CJW, Gant N (2015) Acute hypoxic gas breathing
803 severely impairs cognition and task learning in humans. Physiol & Behaviour, 142, 104
804 – 110.
805 Vaporidi K, Tsatsanis C, Georgopoulos D, Tsichlis PN (2005) Effects of hypoxia and
806 hypercapnia on surfactant protein expression proliferation and apoptosis in A549
807 alveolar epithelial cells. Life Sciences, 78, 284 – 293.
808 Wennmalm A, Benthin G, Edlund A, Jungersten L, Kieler-Jensen N, Lundin S,
809 West JB, Dollery CT, Naimark A (1964) Distribution of blood flow in isolated lung:
810 relation to vascular and alveolar pressures. J Appl Physiol, 19, 713 – 724.
811 West JB (2005) Respiratory Physiology – The Essentials (7th ed.), Lippincott Williams
812 & Wilkins, Maryland, US.
813 West JB, Dollery CT, Naimark A (1964) Distribution of blood flow in isolated lung:
814 relation to vascular and alveolar pressures. J Appl Physiol, 19, 713 – 724.
815 Wettstein D, Moens Y, Jaeggin-Schmucker N, Böhm SH, Rothen HU, Mosing M,
816 Kästner SBR, Schatzmann U (2006) Effects of an alveolar recruitment maneuver on

817 cardiovascular and respiratory parameters during total intravenous anesthesia in ponies.
818 Am J Vet Res, 67 (1), 152 – 159.
819 Whitehair KJ & Willits NH (1999) Predictors of arterial oxygen tension in anesthetized
820 horses: 1,610 cases (1992 – 1994). JAVMA, 215 (7), 978 – 981.
821 Whitehair KJ, Steffey EP, Woliner MJ, Willits NH (1996) Effects of inhalation
822 anesthetic agents on response of horses to three hours of hypoxemia. Am J Vet Res, 57
823 (3), 351 – 360.
824 Young LE, Marlin DJ, McMurphy RM, Walsh K, Dixon PM (1999) Effects of inhaled
825 nitric oxide 10 ppm in spontaneously breathing horses anaesthetized with halothane. Br
826 J Anaesth, 83 (2), 321 – 324.
827 Young SS & Taylor PM (1993) Factors influencing the outcome of equine anaesthesia:
828 a review of 1,314 cases. Equine Vet J, 25, 147–152.
829
830
831